REMARKS/ARGUMENTS

Claims 30, 33, 44-46, 81 and 82 are pending in the subject application. By this Amendment, applicants have cancelled claims 30, 33, 44-46, 81 and 82 without disclaimer or prejudice to applicants' rights to pursue the subject matter of these claims in a later application.

Applicants have also added new claims 87-106. Support for new claims 87-106 may be found, *inter alia*, in the subject specification as follows: Claim 87: page 12, line 33 to page 14, line 11; page 16, line 29 to page 17, line 9; page 18, line 31 to page 19, line 5; Fig. 3; page 27, lines 2-4 and 21-22; page 28, lines 24-30; page 29, line 29 to page 30, line 19; page 39 line 5 to page 40, line 1; page 50 line 2 to page 51, line 6; page 52, lines 6-13; page 58, lines 6-8; page 61, line 27 to page 62, line 12; page 63, lines 6-12, 23-26 and 30-33; Claim 88: page 27, lines 2-7 and 25-28; Claim 89: page 27, lines 7-8 and 26-30; Claim 90: page 27, lines 26-30; Claim 91: page 25, lines 19-22; Claim 92: page 25, lines 19-22; Claim 93: page 25, lines 25-31; Claim 94: page 2, lines 3-5; page 6, lines 20-24; page 42, lines 19-20; Claim 95: page 18, lines 8-10 and line 31 to page 19, line 5; Fig. 3; page 28, lines 24-30; page 29, line 29 to page 30, line 19; page 58, lines 6-8; page 61, line 16 to page 62, line 22; page 63, lines 1-12, 23-26 and 30-33; Claim 96: page 27, lines 2-7 and 25-28; page 69, lines 19-22 and 25-27; Claim 97: 27, lines 7-8 and 26-30; page 69, lines 19-22 and 25-27; Claim 98: page 27, lines 26-30; page 69, lines 19-22 and 25-27; Claim 99: page 25, lines 19-22; Claim 100: page 25, lines 19-22; Claim 101: page 25, lines 25-31; Claim 102: page 22, lines 29-34 (as amended); page 22, line 37 to page 23, line 5 (as amended); page 23, lines 7-12 (as amended); Claim 103: page 22, line 37 to page 23, line 5, as amended in the October 16, 2002 Amendment; Claim 104: page 2, lines 3-5; page 6, lines 20-24; page 42, lines 19-

20; page 61, lines 16-20; page 67, lines 18-21 and 32-34; Claim 105: page 16, lines 21-25; page 49, lines 28-32; and Claim 106: page 34, lines 18-30; page 71, line 30 to page 72, line 8.

Applicants maintain that the new claims do not raise any issue of new matter since they are fully supported by the specification as filed. Accordingly, upon entry of this Amendment, claims 87-106 will be pending.

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 30, 33, 44-46, 81 and 82, under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner stated on page 1, ¶4 of the Office Action that claims 30, 33 and 46 are vague and indefinite in their reference to nucleotide sequences corresponding to SEQ ID NOs.: 12-17. The Examiner noted that SEQ ID NOs.: 13, 15 and 17 represent amino acid sequences, not nucleic acids. The Examiner suggested amending the claims to recite specific SEQ ID NOs. and to identify the subject sequences as nucleotide sequences or amino acids, as appropriate.

In response, applicants note that claims 30, 33 and 46 have been cancelled, thus rendering this rejection moot. Moreover, applicants submit that new claims 102 and 103 recite appropriate SEQ ID NOs. and thus satisfy the requirements of 35 U.S.C. §112, second paragraph.

The Examiner also stated that claims 30, 33, 44-46, 81 and 82 reference mutations that "enhance the stability of the complex" which is allegedly vague and indefinite since the precise regions of gp120/gp41 affected by the mutations are not set forth and the

biochemical nature of the association is not clearly disclosed.

In response, applicants note that this rejection is moot in view of the cancellation of claims 30, 33, 44-46, 81 and 82. In addition, applicants submit that new independent claims 87 and 95 recite both the precise location of the mutations and the type of chemical bond which stabilizes the gp120-gp41 ectodomain interaction. Applicants maintain, therefore, that new claims 87 and 95 and the claims that depend therefrom, meet the requirements of 35 U.S.C. §112, second paragraph.

The Examiner further stated that claims 45 and 82 reference a "complex" which is allegedly vague and indefinite because the precise proteins or molecules involved in this complex are not clearly elucidated.

In response, applicants note that claims 45 and 82 have been cancelled, rendering the rejection thereof moot. Applicants note further that new independent claim 87 recites the precise proteins in the claimed complex. Applicants submit, therefore, that new claim 87 and its dependent claims satisfy the requirements of 35 U.S.C. §112, second paragraph.

Additionally, the Examiner stated that claims 81 and 82 reference proteins "encoded by different nucleic acids" which is allegedly vague and indefinite since the precise structural relationship of the nucleic acids is not readily manifest.

In response, applicants note that this rejection is moot in view of the cancellation of claims 81 and 82, and further that no new claim recites proteins encoded by different nucleic acids.

The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of the claims under 35 U.S.C. §112,

Second Paragraph.

Rejections under 35 U.S.C. §102

The Examiner rejected claims 44 and 45 under 35 U.S.C. §102(a) over Farzan et al. (1998) "Stabilization of Human Immunodeficiency Virus Type 1 Envelope Glycoprotein Trimers by Disulfide Bonds Introduced into the gp41 Glycoprotein Ectodomain," J. Virol. 72(9): 7620-5 ("Farzan"). The Examiner stated on page 3, ¶9 that this reference describes the preparation of stable disulfide-linked HIV-1 gp120/gp41 oligomers, which teaching allegedly meets all of the claimed limitations.

In response, applicants respectfully traverse the Examiner's rejection of claims 44 and 45 under 35 U.S.C. §102. Notwithstanding that the cancellation of claims 44 and 45 renders this rejection moot, applicants wish to address the rejection as it applies to new claims 87-106.

Applicants note that Farzan teaches that "the introduction of cysteine residues at particular locations in the gp41 ectodomain helices can result in the formation of disulfide bonds, stabilizing envelope glycoprotein trimers" (Farzan, page 7621, left column). Applicants emphasize that in Farzan, cysteine residues were introduced solely in the gp41 ectodomain, i.e., not in the gp120 region, of the gp160 polypeptide. These cysteine residues were introduced in the vicinity of "the putative sites of contact between the proposed helical coils in the HIV-1 gp41 ectodomain" (Farzan, page 7621, left column), resulting in the predicted formation of "intersubunit disulfide bonds between the d and e positions of a trimeric coiled coil" (Farzan, page 7622, left column). Farzan further discloses (page 7624, right column) that the formation of these inter-gp41 disulphide bonds results

in the stabilization of dimeric and trimeric forms of a cleavage-defective gp160 glycoprotein.

By contrast, independent claims 87 and 95 recite an invention wherein cysteine residues are introduced at specified positions in both the gp120 and gp41 ectodomain regions, resulting in the formation of disulfide bonds that covalently join the modified gp120 and the modified gp41 ectodomain and thereby stabilize the otherwise non-covalent gp120-gp41 ectodomain interaction. Again, applicants emphasize that this is very different from the introduction of cysteine residues solely into the gp41 ectodomain, resulting in the formation of disulfide bonds that covalently join the modified gp41 ectodomain into oligomeric polypeptides, as taught by Farzan.

Since the invention recited in new claims 87-106 is clearly distinguishable over the disclosure of Farzan, applicants submit that the rejection of any of these claims over the Farzan reference would be unfounded.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 81 and 82 under 35 U.S.C. §103(a) as unpatentable over Farzan in view of U.S. Patent No. 5,474,914, issued December 12, 1995 to Spaete ("Spaete"). The Examiner stated that Farzan et al. describes the preparation of mutant HIV-1 envelope glycoproteins containing additional disulfide residues in gp120 and gp41 that stabilize the association between these proteins. The Examiner also stated that Farzan does not disclose the expression of these proteins on separate plasmids or expression vectors, but that Spate teaches the co-expression of various viral envelope glycoproteins to facilitate functional and biochemical studies. The Examiner therefore concluded that it would have been *prima facie* obvious to one having ordinary skill

in the art at the time the invention was made to express the mutated envelope proteins from separate expression vectors. The Examiner stated that this would provide several useful features such as the ability to perform mutagenesis studies easily on each protein, as well as structural/functional studies involving protein-protein interactions. The Examiner asserted that both the motivation and a reasonable expectation of success were thus present.

In response, applicants respectfully traverse the Examiner's rejection of claims 81 and 82 under 35 U.S.C. §103(a). Notwithstanding that the cancellation of claims 81 and 82 renders this rejection moot, applicants wish to address the rejection as it applies to new claims 87-106.

Applicants note that, according to M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness, and to do so, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge of a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference, or references when combined, must teach or suggest all the claim limitations.

Applicants maintain that the Examiner has failed to satisfy all three prongs of the requirements for establishing a *prima facie* case of obviousness. First, Farzan, in combination with routine skill, does not provide any suggestion or motivation to introduce cysteine residues into <u>both</u> the gp120 and gp41 ectodomain regions of the gp160 polypeptide, so as to form disulfide bonds that covalently join the modified gp120 and the modified gp41 ectodomain and thereby stabilize the gp120-gp41 ectodomain interaction as recited in new independent claims 87 and 95.

Second, Farzan does not provide any expectation of success in making such amino acid modifications. Third, this reference does not teach the claimed element of the modification of both the gp120 and gp41 ectodomain regions of the gp160 polypeptide that enables formation of disulfide bonds between these two regions.

Applicants emphasize again that, contrary to the Examiner's statement on page 4, ¶12, Farzan does not describe the preparation of mutant HIV-1 envelope glycoproteins containing additional disulfide residues in gp120 and gp41 that stabilize the association between these proteins. Instead, as noted above, Farzan teaches the introduction of cysteine residues solely into the gp41 ectodomain helices, resulting in the formation of disulfide bonds that link individual gp41 ectodomain regions in oligomeric forms of a cleavage-defective gp160 glycoprotein.

Applicants note further that the teaching of Spaete is irrelevant to any of the new claims and thus the subject reference does not remedy the above-noted deficiencies of Farzan.

In view of the above, applicants respectfully submit that the rejection of any of claims 87-106 as obvious over Farzan in view of U.S. Patent No. 5,474,914 of Spaete would be without merit as the invention recited by the subject claims is clearly distinguishable over both of these references, taken individually or in combination.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 30 and 33

The Examiner rejected claims 30 and 33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention recited therein.

The Examiner stated on page 5, ¶14 that the claims are directed toward an HIV-1 vaccine comprising SOS gp120/gp41 mutants that contain an intermolecular disulfide bond between the gp120 and gp41 subunits that stabilizes the association between gp120 and gp41. The Examiner stated, however, that the disclosure does not provide any evidence demonstrating that said compositions are capable of preventing HIV-1 transmission or inducing a therapeutic immune response in HIV-1-infected patients.

In response, applicants note that claims 30 and 33 have been cancelled, thus rendering this rejection moot. Applicants note further that none of claims 87-106 is directed to a vaccine.

Claims 44, 45, 81 and 82

The Examiner additionally rejected claims 44, 45, 81 and 82 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Examiner stated on page 7, ¶15 that the claims are broadly directed toward viral envelope proteins carrying "one or more mutations" that "enhance the stability" of the transmembrane (TM) protein and viral surface (SU) protein complex. The Examiner also stated that the disclosure details the preparation of several mutants wherein cysteine residues have been introduced into both gp120 and gp41 to facilitate the association of gp120 and gp41 into a stable complex. The Examiner further stated that

a single double cysteine mutant was identified (A492C/T596C) with the desired properties and designated "SOS gp140." The Examiner additionally stated that a number of other mutants were characterized but were deemed unsuitable for a number of reasons. The Examiner therefore stated that appropriate claim language directed toward the SOS gp140 mutant, or mutants based upon this construct (e.g., SOS gp140 ΔV1V2, SOS gp140 ΔV3) would be acceptable, but that the claim language does not support the full breadth of the claimed invention.

In response, applicants note that claims 44, 45, 81 and 82 have been cancelled, thus rendering this rejection moot. Applicants note further that new independent claims 87 and 95 specify the A492C and T596C mutations in the gp120 and gp41 ectodomain, respectively. Applicants submit, therefore, that claims 87 and 95 and the claims that depend from them satisfy the requirements of 35 U.S.C. §112, first paragraph.

Conclusion

Applicants note that all of the Examiner's rejections have been rendered moot by the cancellation of the pending claims. Moreover, applicants submit that the new claims overcome all of the rejections raised by the Examiner. In view of the remarks and arguments made herein, applicants therefore respectfully request that the Examiner withdraw the claim rejections set forth in the December 16, 2003 Office Action. Applicants further earnestly solicit allowance of new claims 87-106 that will be pending in the subject application upon entry of this Amendment.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone either of them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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